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PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Larg Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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TITLE OF THE INVENTION (280 characters max)

TREATMENT OF PAPILLOMA VIRUS INFECTION

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Respectfully submitted,

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TITLE OF INVENTION

TREATMENT OF PAPILLOMA VIRUS INFECTION

FIELD OF INVENTION

The present invention relates to the treatment of disease caused by papilloma virus infection, in particular to the adjuvant treatment of condylomata acuminata caused by human papilloma virus in men.

BACKGROUND OF THE INVENTION

Human papilloma virus (HPV) infections of the urogenital tract represent the most often sexually transmitted viral disease in man (refs. 1 to 3 - various references are referred to in parenthesis to more fully describe the state of the art to which this invention pertains. Full bibliographic information for each citation is found at the end of the specification, immediately preceding the claims. The disclosure of these references are hereby incorporated by reference into the present disclosure). HPV is a double stranded DNA virus and with the recent developed molecular biological techniques, more than 55 different HPV types have been recognized (ref. 4). HPV is associated with a wide spectrum of clinical states including condylomata acuminata, latent and subclinical infection, and Bowen's disease. Subclinical infections gain more importance as they are believed to cause intraepithelial neoplasia, based on the frequent detection of HPV DNA in invasive carcinomas, especially in urogenital region (refs. 1, 5). A significant risk for the development of an invasive cancer is ascribed to the infections by HPV 16, 18 and 33 (refs. 6 to 9).

The most prevalent HPV types causing condylomata acuminata are type 6 and 11. Condylomata acuminata are visible, multifocal, multicentric and multiform

lesions. Predilection sites are penis, scrotum, perineum, urethra, perianal regions, intertriginous zones, and oral mucosa. In uncircumcised men the frenulum, the coronary sulcus and the inner aspect of the foreskin are most often afflicted, whereas in circumcised patients the shaft of the penis is involved. Genital warts are of great psychological and cosmetic relevance representing a major hindrance to sexual performance.

Treatment options include surgical methods like excision, electrocautery, cryosurgery or laser vaporization. It has been shown in molecular hybridization studies that HPV DNA sequences do exist in adjacent normal tissue after carbon dioxide laser removal of genital warts (ref. 10). These findings and the well known high recurrence rates after initial treatment demonstrate the need for adjuvant therapy to eradicate invisible disease. Therapeutic results with local application of cytotoxic agents, for example, 5-fluorouracil and podophyllin/podophyllotoxin have, however, been unsatisfactory (refs. 11 to 13). Furthermore, several types of interferons (IFN) as well as autologous vaccines have been tried with varying success (refs. 2, 14 to 17). More recently, oral isotretionin has been given with some success to reduce the recurrence rate (refs. 18, 19).

SUMMARY OF INVENTION

In accordance with one aspect of the present invention, there is provided a method of treatment of disease caused by papilloma virus, which comprises applying an effective amount of *Mycobacterium* to the region of infection.

In particular, the present invention in accordance with the treatment of infections caused by human papilloma virus (HPV) using the *Mycobacterium*. Such

infection may include cutaneous and genital warts in man, including verruca vulgaris and condyloma acuminatum, cervical intraepithelial neoplasia and genital carcinomas. The present invention is illustrated by application to recurrent external and intraurethral condylomata acuminata in men.

The *Mycobacterium* which may be employed may be an attenuated form of a *Mycobacterium* of the tuburculosis complex and, in particular, may be an attenuated form of *M. bovis*, specifically Bacillus Calmette-Guerin (BCG).

The treatment may be in effected by application of the *Mycobacterium* in a suitable carrier to the region of infection, which may involve topical application to penile and perianal areas, or intraurethral application to the urogenital tract. The treatment may involve a single or a plurality of doses applied at time intervals. The individual dosage level may be about 1 mg to about 500 mg while the time interval between doses may vary from about 1 to about 30 days. The number of treatments applied is from 1 to about 30 treatments. The treatment may be preceded by laser or other surgical or topical therapy.

The present invention extends, in a further aspect thereof, to the use of a *Mycobacterium* in the manufacture of a medicament for the treatment of infection caused by papilloma virus, particularly human papilloma virus.

GENERAL DESCRIPTION OF INVENTION

A wide spectrum of therapeutic approaches has been used over the past years for the management of condylomata acuminata. However, no form of therapy has yielded consistently effective results. In order to avoid recurrence of disease, the combination of

surgical ablative methods and immunomodulative agents seem to be promising. Due to their antiviral, immunomodulative and antiproliferative properties, interferons have been given as a topical and systemic form of treatment for condylomata acuminata. Interferons were also chosen for their mild side effect profile but recurrence rates up to 75% have been reported (refs. 2, 14 to 17).

In the case studies reported below, patients treated with BCG were cleared of warts and cytological evidence of HPV and had no recurrence of disease. These patients have previously experienced between two and five recurrences of condylomata acuminata. The annual recurrence rate was significantly reduced from 3.2 with standard therapy to 0.75 with BCG therapy. The incidence of side effects due to BCG therapy was low. One patient reported mild dysuria after the second and third BCG application of this first treatment course. Another patient had a penile edema and fever which was managed conservatively. Penile edema is a rare complication after intravesical BCG instillation. However, with intraurethral instillation of BCG for transitional cell carcinoma of the urethra has been reported by Baniel et al (ref. 20). Serious complications like sepsis or hematuria were not observed in the reported group.

EXAMPLE

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Example. This Example are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms

have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

Between October 1994 and March 1997, six men with rapidly recurrent external and intraurethral condylomata acuminata were selected for BCG therapy. The mean age was 27 years (range 22 to 32 years). All patients had previously undergone therapy for recurrent condylomata acuminata in other dermatological and urologic departments (see Table 1 below). The patients were informed they were undergoing an experimental treatment approach and all individuals gave written informed consent.

Examination of the penis and scrotum was performed without and with acetoacid application and lesions were treated with the neodymium:yttrium-aluminum-garnet (ND:YAG) laser (Dornier Medilas Fibertome 4060) at 10 to 20 W. Endoscopic inspection of the urethra and bladder was also performed and visible lesions treated with the Nd:YAG laser. Finally, the perianal region was inspected and laser treatment, when necessary, applied.

A minimum interval of 3 weeks between laser therapy and BCG application was utilized. Internal application for BCG preparation, 81 mg of Connaught strain (Pasteur Mérieux Connaught Canada, North York, Ontario, Canada) were dissolved in 2 ml. Of sterile saline. The solution was directly instilled into the urethra with low pressure and kept for a minimum of 2 hours. To avoid preliminary emptying, a dressing was taped over the meatus. After 2 hours, the dressing was removed and the patient allowed to void spontaneously. A total of six BCG instillations were given in weekly intervals.

External application, eighty-one mg of BCG Connaught strain were dissolved in 2 ml of sterile saline. The solution was given onto a dressing which was gently wrapped around the sulcus and other affected

areas. The dressing was fixed and kept for 2 hours as a moist chamber. This procedure was also repeated six times in weekly intervals.

The courses of six patients are given below and in Table 1 below:

Case 1

A 22-year-old male patient developed condylomata acuminata in 1994. Initially, the frenulum and the meatus were involved. He was treated with local podophyllin but relapsed twice, and was referred to the inventors department in April 1995. Over a period of 13 months, five relapses occurred despite internal and external laser application. From July until October 1996, six intraurethral instillations and external applications of BCG were given in weekly intervals. At follow-up of 11 months, no relapse had been noticed.

Case 2

A 28-year-old male patient demonstrated with perianal and preputial condylomata in May 1995. Cystoscopy revealed additional lesions of the urethra and, therefore, internal and external laser therapy was performed. Three months later an urethral relapse was diagnosed and again treated with laser. Subsequently, the patient received six intraurethral instillations combined with external application of BCG. At follow-up of 29 months, no relapse had been noticed.

Case 3

A 26-year-old male patient had initial diagnosis of condylomata acuminata in 1992. The affected sites included the meatus and frenulum as well as the perianal region. Over a period of 15 months, four relapses occurred which were all managed with laser therapy. In September 1995, intraurethral instillation and external application of BCG was performed. At follow-up of 24 months, no relapse had been noticed.

Case 4

A 32-year-old man developed condylomata acuminata in February 1995. He had a hypospadia without operative correction required. Initial involvement included the meatus, subsequently frenulum and urethra had been involved. During the next 16 months, four relapses were diagnosed and treated with laser. Intraurethral BCG was given in August and September 1996. After 2 further relapses, intraurethral instillation and external application of BCG was repeated in January and February 1997. At follow-up of 8 months, no relapse had been noticed.

Case 5

A 31-year-old male had initial diagnosis of condylomata acuminata in January 1993. Primarily, meatus and foreskin were affected. In the next 27 months, four relapses occurred and managed with laser therapy. The first course of intraurethral instillation and external BCG application was performed in May and June 1995. The patient had three relapses which were treated with laser. In June and July 1996, he received a second course of BCG. He demonstrated one relapse which was lasercoagulated and at follow-up of 12 months, no further relapse had occurred.

Case 6

A 27-year-old male patient demonstrated condylomata acuminata in August 1996. Penis, meatus and urethra were involved. After two relapses, BCG was applied in July 1997. Due to side effects, the treatment was stopped after the third instillation. He had demonstrated a penile edema and fever (38.5°C) and was treated with antiphlogistic drugs and ice packages. At follow-up of 3 months, one new penile lesiion had developed.

In summary of the clinical results obtained, three patients completed one course of BCG. These patients

had no relapse in follow-up studies (Table 1). Two patients underwent a second course of BCG after recurrence of condylomata acuminata. One of them remained without relapse after the second course in a follow-up period of 8 months. The other patient had one relapse after the second BCG course. One patient developed a relapse after he had discontinued therapy due to side effects following the third BCG instillation of his first course.

With respect to side effects, one patient reported mild dysuria after the second and third BCG instillation of his first treatment course. Another patient was withdrawn from BCG therapy due to penile edema and fever. No other side effects were reported.

Before BCG therapy, 36 recurrences of condylomata acuminata were noted in 136 observation months compared to 6 episodes during 96 months after treatment. Therefore, the annual recurrence rate before BCG therapy was 3.2 and 0.75 thereafter. These results were statistically significant ($p<0.05$, test of equality of 2 percentages, (ref. 21).

SUMMARY OF DISCLOSURE

In summary of this disclosure, BCG therapy is useful in treating condylomata acuminata, particularly rapidly recurrent conditions. In general, *Mycobacteria* are useful in treating infections caused by papilloma virus. Modifications are possible within the scope of this invention.

TABLE 1

AGE	No. previous occurences	No. relapses before BCG	No. relapses after BCG	Localisation of replases before BCG	Localisation of relapses after BCG
22	3	5	0	Urethra, frenulum, meatus	
28	1	2	0	foreskin, perianal	
26	5	4	0	frenulum, urethra, meatus	
32	1	4	2,0 after 2nd course	frenulum, urethra, urethra	frenulum, urethra
27	3	4	3,0 after 2nd course	foreskin, meatus urethra	foreskin, meatus urethra
27	1	3	1 (incomplete course)	meatus, urethra	meatus, urethra

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ABSTRACT OF THE DISCLOSURE

Disease caused by papilloma virus is treated by applying an effective amount of *Mycobacterium* to the region of infection. Specifically, condylomata acuminata are caused by human papilloma virus infection. Despite numerous treatment modalities these patients often demonstrate recurrent disease. BCG therapy is used in patients not responding to standard treatment. Six men with rapidly recurrent external and intraurethral condylomata acuminata underwent BCG therapy after initial laser treatment. External application and intraurethral instillation of BCG was performed six times in weekly intervals. Follow-up studies included examination and endoscopic inspection of the urethra and bladder. Three patients completed one course of BCG and had no relapse of condylomata acuminata. Two patients underwent a second course of BCG, of whom one relapsed. One patient relapsed after discontinued therapy due to penile edema. The annual recurrence rate decreased from 3.2 before BCG therapy to 0.75 after BCG therapy ($p<0.05$, test of equality of 2 percentages). The BCG-induced immune response appears to reduce the recurrence rate in patients with condylomata acuminata.